Rejections under the Doctrine of Obviousness-Type Double Patenting

Claims 1-10 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 5,204,108. The Applicant will file a terminal disclaimer upon receipt of a Notice of Allowance of the pending claims.

Claims 11-14 were rejected under the judicially created doctrine of double patenting. As stated above, the Applicant plans to file a terminal disclaimer upon allowance of the claims of the above-referenced application. The Applicant further notes that claims 11-14 in the amended claims are directed to methods and systems wherein a composition is provided for intranasal systemic delivery of a drug, wherein the composition is delivered to the mucosa in a gas stream, and wherein the composition includes a drug associated with microspheres having a diameter between 0.1 and 10 μm. The methods and systems defined by claims 11-14 are not obvious in view of the compositions for transmucosal delivery claimed in U.S. Patent No. 5,204,108. The claims of U.S. Patent No. 5,204,108 are directed to microspheres adapted to gel in contact with the mucosal surface which are associated with a peptide having a maximum molecular weight of 6000, wherein the microspheres are made of starch, gelatin, collagen or dextran. The methods and compositions defined by the amended claims thus are distinguishable over the compositions claimed in U.S. Patent No. 5,204,108.

Rejections Under 35 U.S.C. § 112

Claims 1-2 and 5-14 were rejected under 35 U.S.C. § 112, first paragraph, as being enabled only for the material in claim 3. The Applicant respectfully traverses this rejection. Claim 3 as amended recites microspheres which include starch, gelatin, albumin, collagen or dextran. The compositions recited in the claims and disclosed in the specification include bioadhesive microspheres with a diameter between 0.1 and 10 μm associated with an active drug, wherein the compositions are capable of being administered intranasally and of delivering systemically a therapeutically effective amount of the drug. The specification gives a variety of examples of suitable materials including but not limited to the materials recited in claim 3. For example, the microspheres can be made of poly(vinyl alcohol), polylactide-co-glycolide, hyaluronic acid or derivatives thereof (page 5, lines 16-18 of the specification). The preparation of hyaluronic acid ester microspheres is disclosed on page 7 of the specification. Similarly, other suitable materials can be selected with only routine screening. Enablement is not precluded by the requirement for some routine experimentation or screening. *In re Wands*, 858 F2d. 731 (Fed. Cir. 1988). One of ordinary skill in the art could readily select other suitable bioadhesive materials with only routine experimentation. The Applicant accordingly submits that the claims as amended herein are fully enabled in accordance with the requirements of 35 U.S.C. § 112, first paragraph.

Claims 3-4, 6 and 8 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 3 has been amended to delete the recitation of the term

"derivatives". Claim 6 has been amended to recite a drug delivery composition which has been "treated by heating" to more clearly recite the claimed composition. Applicant notes that claim 8 was amended in the parent application in an Amendment filed March 21, 1994 to delete the recitation of the specific compounds, and to recite an absorption enhancer which is a "surfactant". Accordingly, the Applicant requests that the rejections under 35 U.S.C. § 112, second paragraph be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1-5, 11 and 13 were rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 4,847,091 to Illum, ("Illum"). The Applicant respectfully traverses this rejection to the extent that it is maintained over the claims as amended herein.

Illum discloses microspheres incorporating sodium cromoglycate which are formed of a material having ion exchange properties. The disclosure of Illum is limited to the synthesis of microspheres incorporating sodium cromoglycate and the use of the microspheres for local treatment. Illum discloses that the microspheres can be used for treatment of allergic conditions. For example, Illum discloses treatment of conditions of the outer eye such as hay fever or conjunctivitis (col. 3, lines 3-20), conditions of the nose such as perennial rhinitis, and conditions of the lung such as asthma. The disclosure of Illum thus is limited to the administration of microspheres for localized treatment of a condition. Nothing in Illum teaches or suggests the use of the sodium cromoglycate containing microspheres for systemic therapeutic treatment.

As noted in the Applicant's Supplemental Response filed May 26, 1994 in the parent application, sodium cromoglycate is poorly absorbed and not useful for systemic treatment. Rather, sodium cromoglycate is used therapeutically for local treatment. As indicated in the Supplemental Response filed May 26, 1994, and in the documents cofiled therewith, sodium cromoglycate is poorly absorbed from the gastrointestinal tract and therefore is only effective when administered for local action. It is used for the treatment of asthma, rhinitis and nasal congestion, which are clearly local uses. Nothing in Illum suggests or teaches systemic delivery of a drug using the microspheres. Illum in fact teaches away from systemic delivery by suggesting only local administration.

Nothing in the disclosure of Illum suggests that the microspheres are capable of systemic delivery. Nothing in Illum suggests that intranasally administered sodium cromoglycate penetrates nasal tissue and enters the body and is capable of causing a systemic therapeutic effect. Rather, as indicated in Applicant's Supplemental Response filed May 26, 1994, sodium cromoglycate is known to those skilled in the art to be poorly absorbed and to be therapeutically effective only when administered topically for local action. In order for a rejection under 35 U.S.C. § 102 to be proper, all of the material elements of the claims must be present in one prior art source. *In re Marshall* (CCPA 1978) 577 F2d 301. As amended, independent claims 1 and 17 recite compositions including microcapsules which are capable of systemic delivery of a therapeutic amount of a drug when administered intranasally, which is not disclosed in Illum.

Nothing in Illum suggests the methods and compositions defined by the precise limitations of the independent claims. Additionally, nothing in Illum suggests the methods and compositions defined by the dependent claims, wherein, for example, the drug is a biologically active peptide such as insulin. The Applicant has demonstrated the synthesis and use of compositions including microspheres which are capable of systemic delivery of a therapeutically effective amount of a drug in a mammal. The Applicant further has provided experimental results which show that the compositions are therapeutically effective systemically. For example, the compositions can be intranasally administered to systemically deliver insulin to sheep in a therapeutically effective amount to reduce plasma glucose (see Example 3 and, particularly, page 26 of the specification).

Nothing in Illum teaches or suggests microspheres which are capable of systemic delivery of a therapeutically effective amount of a drug as recited in the amended claims. Illum thus does not identically disclose the claimed subject matter, as is required for a proper rejection under 35 U.S.C. § 102. *In re Arkley et al.*, 172 USPQ 524, 526 (CCPA, 1972). Accordingly, the Applicant requests that the outstanding rejections under § 102 be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 1-14 were rejected under 35 U.S.C. § 103 as being obvious over Illum, L., *Nato ASI Symposium*, 125:205-210 (1986) "Illum (1986)". Claims 7-12 and 14 were rejected under 35 U.S.C. § 103 as being obvious over Illum or Illum (1986) in view of Hanson *et*

al., *Advanced Delivery Systems for Peptides and Proteins*, p. 233-242 (1988) "Hanson", or Salzman *et al.*, *New Eng. J. Med.*, 312:1078-1084 (1985) ("Salzman") and vice versa.

Illum (1986) discloses albumin starch microspheres for use in nasal administration. The preferred size range of the microspheres is 40-60 μm (page 207 of Illum 1986). Illum (1986) does not teach or suggest the use of microspheres having a diameter less than 20 μm for use in intranasal delivery. Nothing in Illum (1986) would have motivated one of ordinary skill in the art to make or use the claimed microspheres which have a diameter between 0.1 μm and 10 μm. Illum (1986), in fact, teaches away from the claimed microparticles by suggesting specifically the use of microspheres with a size of 40-60 μm. In view of Illum (1986), there would have been no motivation to make the claimed microspheres. The Applicant has demonstrated that, unexpectedly, improved systemic therapeutic results are obtained by intranasal administration of microspheres having a diameter less than 10 μm, which is not suggested in the cited art (see Example 1 of the specification).

Hanson discloses that the biological response to nasal administration of calcitonin can be increased by the addition of various surfactants. Salzman discloses that intranasal absorption of insulin can be increased in the presence of a non-ionic detergent. Nothing in either Hanson or Salzman teaches or suggests the formation or use of the claimed composition including bioadhesive microspheres which have a diameter between 0.1 to 10 μm for the intranasal administration and systemic delivery of a drug. In order to make a

determination of obviousness under 35 U.S.C. § 103, the prior art must suggest the invention claimed. *In re Dow Chemical Company*, 837 F.2d 469 (Fed. Cir. 1988); *In re Geiger*, 815 F.2d 686 (Fed. Cir. 1987). Nothing in Hanson or Salzman provides any suggestion of the claimed compositions including microspheres, or provides any teaching of methods for making or using the compositions, or any suggestion that they would provide the beneficial effects shown by the Applicant.

Nothing in Hanson or Salzman, alone or in combination with Illum or Illum (1986) provides any teaching or suggestion of the claimed compositions including microspheres for intranasal administration and systemic delivery of a therapeutically effective amount of a drug. Both the suggestion to make the claimed composition or device or carry out the claimed process and the reasonable expectation of success must be found in the prior art, not in the Applicant's disclosure. *In re Vaeck* (CAFC 1991) 947 F.2d 488, 20 PQ2d 1438. Nothing in the combined cited art suggests the unexpected results discovered by the Applicant. Nothing in the applied art would have suggest the Applicant's claimed methods to one of ordinary skill in the art. In order to make a determination of obviousness under 35 U.S.C. § 103, the prior art, viewed by itself and not in retrospect, must suggest doing what the Applicant has done. *In re Shaffer* (CCPA 1956) 229 F.2d 476, 108 USPQ 326; *In re Skoll* (CCPA 1975) 523 F.2d 1392, 187 USPQ 481. The applied art, viewed alone or in combination, would not have suggested the methods and compositions defined by the amended claims to one of ordinary skill in the art, in the absence of hindsight.

Nothing in the applied art suggests the claimed compositions, including microspheres with a diameter between 0.1 and 10 μm and an active drug, which can be intranasally administered to systemically deliver a therapeutically effective amount of the drug to a mammal, as recited in the amended independent claims 1 and 17. Similarly, nothing in the applied art alone or in combination suggests the embodiments defined by the dependent claims wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface (claims 2 and 18), or wherein the microspheres are formed from starch (claims 4 and 20) or certain modified starches (claims 16 and 28). The applied art also does not teach or suggest the compositions defined by the limitations of dependent claims 9-10 and 25-26, wherein the composition includes microspheres and a biologically active peptide such as insulin or calcitonin, and wherein the composition is capable of systemic delivery of a therapeutically active amount of the peptide upon intranasal administration.

Since the applied art, considered either alone or in combination, does not suggest the methods and compositions defined by the limitations of the claims as amended herein, the Applicant requests that the rejections under 35 U.S.C. § 103 be withdrawn.

Conclusion

For all of the forgoing reasons, allowance of each of the pending claims 1-28 as amended herein is respectfully solicited.

Respectfully submitted,

Madeline Johnston

Madeline I. Johnston, Ph.D.
Registration No. 36,174

Date: September 18, 1995

ARNALL GOLDEN & GREGORY
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8798
(404 873-8599 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Robb Copeland

Date: September 18, 1995

APPENDIX
Claims as Amended

1. (Amended) [In a] A particulate drug delivery composition for intranasal delivery comprising a plurality of bioadhesive microspheres and a systemically active drug, [the improvement comprising that] wherein at least 90 wt % of the microspheres of the composition have a diameter of between 0.1 μm and 10 μm, and wherein the composition is capable of systemic delivery of a therapeutically effective amount of the drug to a mammal upon intranasal administration.

2. A drug delivery composition according to Claim 1 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

3. (Amended) A drug delivery composition according to Claim 1 or 2 wherein the microspheres comprise starch, [starch derivatives,] gelatin, albumin, collagen, or dextran [or dextran derivatives].

4. A drug delivery composition according to Claim 3 wherein the microspheres are starch microspheres.

5. A drug delivery composition according to Claim 1 wherein the microsphere material is cross-linked.

6. (Amended) A drug delivery composition according to Claim 1 wherein the microspheres have been [stabilised by heat treatment] treated by heating.

7. A drug delivery composition according to Claim 1 additionally comprising an absorption enhancer.

8. A drug delivery composition according to Claim 7 wherein the absorption enhancer is a surfactant.

9. A drug delivery composition according to Claim 1 wherein the drug is a biologically active peptide.

10. A drug delivery composition according to Claim 9 wherein the peptide is insulin or calcitonin.

11. A system for intranasal drug delivery comprising a drug delivery composition according to Claim 1 and a container having an orifice through which the composition can be delivered to the nasal mucosa in a gas stream.

12. A system according to Claim 11 wherein the system is such that, in use, the product of the flow rate and the square of the microsphere aerodynamic diameter is greater than 2000 μm^2.litres/min.

13. A method of delivering a drug to the nasal mucosa, comprising introducing a gas stream containing a composition according to Claim 1 into the nose.

14. A method of treating diabetes comprising introducing a gas stream containing a composition according to Claim 1 wherein the systemically active drug is insulin into the nose.

15. (New) The drug delivery composition of claim 1 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

16. (New) The drug delivery composition of claim 1 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.

17. (New) A method for systemically delivering an active drug to a mammal, the method comprising:

a) providing a composition comprising a plurality of bioadhesive microspheres and an active drug, wherein at least 90 wt % of the microspheres in the composition have a diameter between 0.1 μm and 10 μm; and

b) administering the composition to a mammal intranasally thereby to systemically delivery a therapeutically effective amount of the drug to the mammal.

18. (New) The method of claim 17 wherein the microspheres are prepared from a material that will gel in contact with the mucosal surface.

19. (New) The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of starch, gelatin, albumin, collagen and dextran.

20. (New) The method of claim 19 wherein the microspheres comprise starch.

21. (New) The method of claim 17 wherein the microsphere material is cross-linked prior to step b).

22. (New) The method of claim 17 wherein the microspheres are treated by heating prior to step b).

23. (New) The method of claim 17 the composition provided in step a) further comprises an absorption enhancer.

24. (New) The method of claim 23 wherein the absorption enhancer is a surfactant.

25. (New) The method of claim 17 wherein the drug is a biologically active peptide.

26. (New) The method of claim 25 wherein the peptide is insulin or calcitonin.

27. (New) The method of claim 17 wherein the microspheres comprise a material or ester thereof selected from the group consisting of polyvinyl alcohol, polylactide-co-glycolide, hyaluronic acid, gellan gum and pectin.

28. (New) The method of claim 17 wherein the microspheres comprise a material selected from the group consisting of hydroxyethyl starch, hydroxypropyl starch, carboxymethyl starch, cationic starch, acetylated starch, phosphorylated starch and grafted starch.